

## REMARKS

Claims 1-3, 5-7 and 10-21 are now in the application. Claims 1 and 20 have been amended to further define the water-soluble organic solvent. The amendments to the claims find support in the specification, for instance, at page 4, lines 1 to 13 for the recitation "highly miscible with water", at page 6, line 24 to page 7, line 3; page 7 line 33 to page 8, line 8 for the claimed Markush group of the water-soluble organic solvent; and page 8, lines 18 to 21 for the recitation "at least one". In view of the amendment to claim 1, claim 4 has been cancelled without prejudice or disclaimer and the dependency of claims 5 and 12 have been changed to claim 1. Also, claims 2 and 6 for consistency with the amendments to claim 1. The amendments to the claims do not introduce any new matter.

Claims 1-7 and 10-21 were rejected under 35 USC 103(a) as being unpatentable over GB 947643 to Merck et al. and applicants' acknowledged prior art in view of US Patent 4,061,660 to Kijima et al., US Patent 4,039,573 to Kijima et al. and US Patent 4,163,864 to Morita et al., International Publication No. WO 03/006509 and International Publication No. WO 03/006411. The cited references fail to render obvious the present.

Before addressing the rejection over the cited art, a discussion of the present invention would be helpful. In particular, the present invention is directed to a process of purifying reduced coenzyme Q<sub>10</sub>. According to the present invention, a water-soluble organic solvent or a mixed solvent composed of a water-soluble organic solvent and water is used to wash crystals and/or oil of reduced coenzyme Q<sub>10</sub>, and a water-soluble impurity derived from the reducing agent such as hyposulfurous acid or ascorbic acids is thereby removed. A distinctive feature of the present invention is that a water-soluble organic solvent or a mixed solvent composed of a water-soluble organic solvent and water is used for washing. In order to remove impurities highly soluble in water such as hyposulfurous acid, ascorbic acids and derivatives thereof, those skilled in the art would use water for washing. However, as previously explained in prior responses, impurities cannot be sufficiently removed when water is used for washing crystals and/or oil of reduced coenzyme Q<sub>10</sub>. Those skilled in the art would not expect that water-soluble organic solvents are much more effective than water for removing water-soluble impurities.

GB 947643 to Merck & Co fails to suggest the present invention since, among other things, as appreciated by the examiner, GB 947643 does not even imply washing of the crystals. Moreover, the product therein, as recognized by the examiner, would necessarily contain water-insoluble impurities such as the reducing agent and/or derivatives derived from the reducing agent. The secondary references do not overcome the deficiencies of GB 947643 with respect to rendering unpatentable the present invention.

The Office Action does not provide the adequate rationale or reasoning as to why persons skilled in the art would wash crystals and/or oil with a water-soluble organic solvent. As already discussed in previous responses, the secondary references do not teach washing crystals.

With respect to washing, it seems that the Office Action considers recrystallization with an alcohol-petroleum ether mixture as suggested in Merck & Co as corresponding to the washing of crystals according to the present invention.

Recrystallization and washing of crystals/oil according to the present invention are different procedures. Superficially, they might look similar but only because they both remove impurities. Recrystallization is a separation of a desired compound from impurities, both of which are present in a mother liquor, leaving as much impurities as possible in the mother liquor. On the other hand, washing of crystals removes impurities which remain in or on the crystals, e.g. adhere to the surface of crystals.

Further, it should be noted that a water-soluble impurity cannot be sufficiently removed by crystallization. As shown in Production Example 1 of the present application, crystals of reduced coenzyme Q<sub>10</sub> were obtained by a crystallization from a mixed solvent composed of ethanol and water, but it contains 3.2% of L-ascorbic acid and 0.36% of oxalic acid. On the other hand, as shown in Examples, the impurity can be removed easily by washing the crystals.

The Office Action cites the secondary references with respect to washing of crystals with water soluble organic solvents. The secondary references do not overcome the above discussed deficiencies of Merck & Co with respect to rendering unpatentable the present invention.

With respect to WO 03/006509 and WO 03/006411, attached is a verified English translation of applicant's Japanese priority application 2003-005151 filed January 10, 2003, which is prior to the publication date of both WO 03/006509 and WO 03/006411 of January 25, 2003. Since the present application is the US National Stage of PCT/JP04/00117, filed January 9, 2004, the filing date of this application is January 9, 2004, less than one year after the publication date of WO 03/006509 and WO 03/006411. Accordingly, WO 03/006509 and WO 03/006411 are not available as prior art against the present invention. The filing of the verified English translation of applicant's Japanese priority application 2003-005151 is not to be construed as an admission, estoppel or acquiescence. See *Credle v. Bond* 23 F. 3d 1566; 30 USPQ 2d. 1911 (Fed. Cir. 1994) and *Greenwood v. Hattori Seiko Co. Ltd.* 14 USPQ2d 1474, (Fed. Cir. 1990).

The Office Action considers that US Patent 4,061,660 to Kijima et al. (hereinafter also referred to as "Kijima '660") teaches washing of crystals with diethyl ether in Example 1. In Example 1 of Kijima '660, silica-alumina was added to the reaction mixture (col. 4, lines 40 to 43). After completion of the reaction, the reaction mixture was filtered, and the filtered solids were washed with diethyl ether. This means that the filtered solids including silica-alumina were washed to collect a desired product which adhered to the surface of the solids. Those skilled in the art would readily understand that the washing is not for removal of impurity from a desired product.

The Office Action considers that US Patent 4,039,573 to Kijima et al (hereinafter also referred to as "Kijima '573") teaches a washing process where zinc is the catalyst in Example 3. First of all, a water-soluble organic solvent is not used for washing in Example 3 of Kijima '573. Further, the procedure does not include a washing of a desired product in the form of crystals or oil. Kijima '573 teaches that the filtrate was washed with water and then with a weak-caustic soda aqueous solution. Namely the reference teaches washing the solution of a desired product.

The Office Action considers that US Patent 4,163,864 to Morita et al. (hereinafter also referred to as "Morita") shows a washing process in Example 1 where methanol is used for washing. In Example 1 of Morita, the reaction mixture was subjected to filtration, the filtrate was

washed with a methanolic aqueous sodium hydroxide solution and then with an aqueous methanol solution (please see col. 4, lines 31 to 36). Therefore, the reference teaches washing the filtrate liquor, namely a solution of a desired product. The procedure does not include washing of a desired product in the form of crystals or oil.

As explained above, none of Kijima '660, Kijima '573 and Morita teaches washing crystals and/or oil of a desired product to thereby remove a water-soluble impurity.

With respect to “impurity”, all the of the cited references are silent about the water-soluble impurity specified in claim 1, namely a reducing agent selected from the group consisting of hyposulfurous acid, hyposulfurous acid salts, ascorbic acids, esters of ascorbic acids or salts of ascorbic acids, or an impurity derived from the reducing agent.

Concerning the solvent, Merck & Co teaches using an alcohol-petroleum ether mixture for recrystallization. Kijima '660 uses diethyl ether and Kijima '573 uses water for washing. None of them teach use the washing solvent specified in claim 1.

The Office Action considers that it is a common practice to use suitable solvents for washing/purifying the crystals (page 4, lines 4 to 5).

When removing impurities highly soluble in water such as hyposulfurous acid, ascorbic acids and derivative thereof, those skilled in the art would naturally choose water as a washing solvent.

However, impurities cannot be removed sufficiently when water is used for washing crystals and/or oil of reduced coenzyme Q<sub>10</sub>. In Example 1 of the present application, crystals of reduced coenzyme Q<sub>10</sub> (containing 3.2% of L-ascorbic acid and 0.36% of oxalic acid) obtained in Production Example 1 were each washed with aqueous ethanol solutions (mixtures of ethanol and water). As shown in Table 1, after washing, contents of L-ascorbic acid were 0.07% or less and contents of oxalic acid were 0.05% or less. On the other hand, in Comparative Example 1 where water was used for washing, content of L-ascorbic acid was 0.18% and content of oxalic acid was 0.15%. Such results are not expected. Accordingly, those skilled in the art would not

choose the washing solvent specified in claim 1, and even if they would, the effect of the solvent cannot be expected.

Since the secondary references are silent about impurities derived from hyposulfurous acid, hyposulfurous acid salts, ascorbic acids, esters of ascorbic acids or salts of ascorbic acids and since they do not disclose washing crystals or oil, it is not at all apparent why the cited references would render obvious the present invention. The rejection relies upon impermissible “hindsight”.

In the Office Action, the examiner commented that absent any showing of unusual and/or unexpected results, the art obtains the same effect on the purification of reduced coenzyme Q<sub>10</sub>. However, since a *prima facie* case of obviousness has not even been established, comparative experiments or a showing of unexpected results are not actually needed in this application. Please see *Takeda v. Alphapharm*, 492 F. 3d 1350 (Fed. Cir. 2007). Nevertheless, as discussed above, the present application already includes comparative examples that illustrate the unexpected results obtained from the process of the present invention. Furthermore, please see the previously filed Declaration by Mr. Ueda and the partial translation of *Kagaku Binran* (Handbook of Chemistry), which further support the non-obviousness of the present invention. All evidence must be considered in evaluating the non-obviousness of the invention. Please see *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727; 82 USPQ2d 1385 (2007) and *In re Sullivan*, 498 F. 3d 1345 (Fed. Cir. 2007). Furthermore, when evidence of non-obviousness is present, the Office should reconsider any initial obviousness determination in view of the entire record. Please see *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984) and *In re Eli Lilly & Co.*, 14 USPQ2d 943 (Fed. Cir. 1990) and Examiner's Guidelines Update: Developments after *KSR v. Teleflex*, Federal Register/Vol. 75, No. 169/Wednesday, September 1, 2010/Notices page 53657.

Also, the prior art should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. See *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 46 (Fed. Cir. 1986).

Accordingly, the present invention is not rendered obvious GB 947643 to Merck et al. in view of US Patent 4,061,660 to Kijima et al., US Patent 4,039,573 to Kijima et al. and US Patent 4,163,864 to Morita et al.

The mere fact that the cited art may be modified in the manner suggested in the Office Action does not make this modification obvious, unless the cited art suggest the desirability of the modification or there is well reasoned and articulated rationale to do so. This is not present in the present record. The Examiner's attention is kindly directed to *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727; 82 USPQ2d 1385 (2007), *In re Lee* 61 USPQ2d 1430 (Fed. Cir. 2002), *In re Dembiczak et al.* 50 USPQ2d. 1614 (Fed. Cir. 1999), *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984), *In re Laskowski*, 10 USPQ2d. 1397 (Fed. Cir. 1989) and *In re Fritch*, 23, USPQ2d. 1780 (Fed. Cir. 1992).

Also, the cited art lacks the necessary direction or incentive to those of ordinary skill in the art to render a rejection under 35 USC 103 sustainable. The cited art fails to provide the degree of predictability of success of achieving the properties attainable by the present invention needed to sustain a rejection under 35 USC 103. See *KSR Int'l Co. v. Teleflex, Inc.*, supra, *Diversitech Corp. v. Century Steps, Inc.* 7 USPQ2d 1315 (Fed. Cir. 1988), *In re Mercier*, 187 USPQ 774 (CCPA 1975) and *In re Naylor*, 152 USPQ 106 (CCPA 1966).

Moreover, the properties of the subject matter and improvements which are inherent in the claimed subject matter and disclosed in the specification are to be considered when evaluating the question of obviousness under 35 USC 103. See *KSR Int'l Co. v. Teleflex, Inc.*, supra; *In re Sullivan*, 498 F. 3d 1345 (Fed. Cir. 2007), *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d. 1923 (Fed. Cir. 1990), *In re Antonie*, 195, USPQ 6 (CCPA 1977), *In re Estes*, 164 USPQ 519 (CCPA 1970), and *In re Papesch*, 137 USPQ 43 (CCPA 1963).

No property can be ignored in determining patentability and comparing the claimed invention to the cited art. Along these lines, see *In re Sullivan*, supra, *In re Papesch*, supra, *In re*

*Burt et al*, 148 USPQ 548 (CCPA 1966), *In re Ward*, 141 USPQ 227 (CCPA 1964), and *In re Cescon*, 177 USPQ 264 (CCPA 1973).

In view of the above, consideration and allowance are respectfully solicited.

In the event the Examiner believes an interview might serve in any way to advance the prosecution of this application, the undersigned is available at the telephone number noted below.

The Office is authorized to charge any necessary fees to Deposit Account No. 22-0185, under Order No. 21581-00496-US from which the undersigned is authorized to draw.

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